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The distribution of neoplasia arising on the cervix: Results from the ALTS trial

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Objective: This study was undertaken to evaluate the topographic distribution of precancerous intraepithelial lesions on the cervix.
Study design: We studied the distribution of cervical biopsies and location of acetowhite lesions as determined by cervigrams among women who underwent a colposcopic examination and biopsy during the ASCUS-LSIL Triage Study (ALTS).
Results: More biopsies were taken in the 12 o'clock (41.4%) and 6 o'clock (28.4%) quadrants than in 3 o'clock and 9 o'clock quadrant (15.8% and 14.5%, respectively) ($P < .001$). The proportion of abnormal histology per biopsy, and the grade of neoplasia, did not vary significantly by position. Cervigrams demonstrated visible intraepithelial lesions and acetowhitening more common on the anterior and posterior quadrants of the cervix.
Conclusion: More cervical intraepithelial neoplasia might develop at the anterior and posterior lips of the cervix. However, the evidence is weak and confounded by a tendency of the anterior and posterior quadrants to be acetowhite even in the absence of cervical intraepithelial neoplasia.

The last 2 decades of cervical cancer research have clarified the natural history and central causal role of human papillomavirus (HPV) infection.[1] As a result, we now have an improved understanding of cervical carcinogenesis,[2] improved screening protocols,[3] and new strategies for management of the commonly diagnosed, mildly abnormal and equivocal cervical lesions.[4,5] However, the cornerstone of clinical management remains colposcopic examination with guided biopsy. Colposcopy is used for the evaluation of patients with abnormal cytology or symptoms suggesting cervical cancer regardless of cytological results, and for follow-up after

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treatment of cervical intraepithelial neoplasia (CIN). The main role of colposcopy is to locate abnormal-appearing lesions and to direct biopsies to areas in which a higher grade of disease (CIN 2, CIN 3, or invasive cancer) is suspected.

There is a considerable ongoing scientific research to improve the diagnostic accuracy of colposcopy using new technology such as spectral analysis and computer models.[6] But colposcopy itself has not been optimized by formal study, partly because of the difficulty of recording adequate visual images. Much of instruction in colposcopy is informal mentorship based on the teacher's experience. We are attempting to formalize the study of colposcopy using the accumulated visual images from National Cancer Institute-funded studies.[7,8]

For example, we noted that there is a lack of data with regard to a simple observation accepted anecdotally by many clinicians: that the distribution of cervical lesions does not appear to be uniformly distributed around the circumference of the cervix; rather there is an increased frequency of biopsies of the anterior and posterior lips of the cervix.

Understanding the distribution of cervical lesions may shed some light on the pathophysiology of the disease process. A true predominance of lesions at the anterior and posterior lips could reflect several biologic processes: (1) during fetal development and until the adolescent years, the anterior and posterior lips undergo later squamous transformation than the lateral lips, exposing "vulnerable" tissue longer; (2) HPV infection could be more common because of the penis causing more sexual microtrauma in the anterior and posterior positions; or (3) there might be decreased viral clearance because of less blood flow from the blood supply that flows in laterally along the broad ligaments. On the other hand, the observed anterior-posterior predominance could be an artifact of mechanical ease of biopsy.

This study was undertaken to address the issue of the topographic distribution of lesions, particularly CIN 3 lesions. We chose to study women enrolled in the ASCUS-LSIL Triage Study (ALTS), which provides a well-studied and documented source of CIN of different grades from 4 diverse clinical centers.

Material and methods

Study population and ALTS protocol

As described in detail elsewhere,[7,9] ALTS was a large multicenter, randomized, prospective study designed to evaluate 3 alternative methods of management and treatment of women referred with atypical squamous cells of undetermined significance (ASCUS) (n = 3488) and low-grade intraepithelial neoplasia (LSIL) (n = 1572) cytology. There were 3 randomization arms at enrollment: immediate colposcopy; HPV triage to colposcopy using Hybrid Capture 2 (HC2, Digene Co., Gaithersburg, MD) that targets 13 oncogenic HPV types; and conservative management based on repeated cytology with colposcopic referral at an high-grade intraepithelial neoplasia (HSIL) threshold. Liquid-based cytology (Cytyc Co, Marlborough, MA), additional cervical cells for HPV typing, and cervigrams (duplicate, magnified photographs of the cervix) were taken at enrollment and follow-up visits. Thus, the subjects who were enrolled in the immediate colposcopy arm of the study had their enrollment cervigram and colposcopic examination conducted on the same day. Study subjects in the other two study arms did not have a repeat cervigram conducted if they were triaged to colposcopy (performed on average 50-60 days later).

Regardless of study arm, following the enrollment visit, all women were followed every 6 months by cytology and underwent exit colposcopy at 2 years. Participation rates exceeded 80%. Loop electrosurgical excision procedure (LEEP) was conducted on women diagnosed at any visit with CIN 2 or worse histopathology or, at exit, for those with persistent lower-grade lesions. The randomization aspect of this clinical trial was not relevant to the current analysis; thus, we present data combined across referral cytologic interpretations and study arms. For this analysis, the study population included women who underwent a colposcopic examination and biopsy during the enrollment phase of ALTS.

Histology data

The primary analysis focused on enrollment colposcopically directed biopsies. Biopsy location was recorded systematically for all patients. Histologic diagnoses were rendered by a pathology quality control group according to consensus protocols, as described in detail elsewhere.[7,10] Although LEEP specimens, when available, may have provided more complete sampling of the cervix, the lack of spatial orientation and nonuniform processing of the specimens precluded correlation of histology with precise o'clock positions.

For the secondary analysis using cervigrams to assess acetowhitening by o'clock position and histologic diagnosis, we were especially concerned about possibly missed prevalent disease; therefore, the cumulative worst histology during the 2 years of the trial was used. This is consistent with previous ALTS analyses in which CIN 3 diagnosed during follow-up is considered prevalent disease.[11,12]

Colposcopists involved in the trial underwent standardized training by a colposcopy quality control group prior to the initiation of the trial. The majority of the colposcopies (64%) were performed by physicians and 36% by a nurse-practitioner. Colposcopists were instructed to biopsy the most severe lesion. There were no restrictions on the number of colposcopic biopsies performed (range 1-4). A patient with a normal-appearing cervix did not require a cervical biopsy.

Biopsy location was assigned using the o'clock position for each biopsy with the 12 o'clock position located at the midpoint of the anterior lip of the cervix, the 6 o'clock position being located at the midpoint of the posterior lip, and the 3 o'clock and 9 o'clock position located on the patients' left and right side, respectively. For the analysis of the topography of lesions, we divided the cervix into 4 quadrants centered on the 12 o'clock, 3 o'clock, 6 o'clock, and 9 o'clock positions. Biopsies taken from 11 o'clock, 12 o'clock, and 1 o'clock positions were included in the 12 o'clock quadrant. Biopsies taken from the 2 o'clock, 3 o'clock, and 4 o'clock positions were assigned to the 3 o'clock quadrant. Similar assignments were conducted for the 6 o'clock and 9 o'clock quadrants (Figure).

HPV data and cervigrams

To define the HPV infection status of participants, we supplemented data from HC2, which uses a pooled probe of 13 types, with HPV typing for 38 individual types of HPV based on a prototype linear array assay (Roche Molecular Systems, Alameda, CA) as described elsewhere.[7] The 2 kinds of HPV testing permitted us to divide participants according to viral status.

We stratified women by viral status and histologic diagnoses and selected a random sample of cervigrams obtained prior to colposcopy as a proxy for what colposcopists likely saw at the time of colposcopically directed biopsy. These data on visual appearance for each o'clock position of the cervix were used to supplement the biopsy position data.

From the population of women who attended colposcopy during the ALTS enrollment period, we selected 100 of the 227 patients with normal histology and negative polymerase chain reaction (PCR) and HC2 tests; of note, 32 of the 100 had ASCUS or LSIL ThinPrep (Cytyc Co, Marlborough, MA) interpretations on the same day as their HPV testing, but none had HSIL. We chose 100 of the 409 patients with normal histology who were positive by both HC2 and PCR for at least 1 oncogenic HPV type to explore the visual appearance of HPV infection confirmed by molecular testing; although biopsies were normal, the majority of them had equivocal or mild cytologic changes. We evaluated the cervigrams of 100 of the 387 patients with definite low-grade lesions, defined as histology of CIN 1 and positive by HC2 and PCR for oncogenic types at enrollment; only 1 patient had a ThinPrep result of CIN 3 at enrollment. Finally, we evaluated 108 of the 542 patients with tissue-confirmed CIN 3 diagnosed at any point during the 2 years of the study. All these cervigrams were randomly selected.

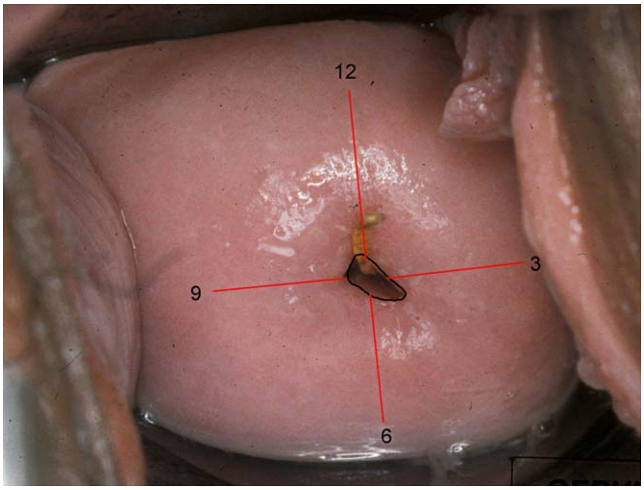

Figure Cervix clockwise divided starting on the external os.

During the review of the cervigram, the external os was identified, and the cervix was divided as a clock face (Figure). Each one of the o'clock areas of the cervix was reviewed for any lesion. A region was considered positive if an area of acetowhiting compatible with cervical intraepithelial neoplasia was found and negative when the area contained only mature metaplasia or normal epithelium. A region was considered inadequate for evaluation if there was poor picture quality or obscuring blood or mucus or the orientation of the cervix did not permit evaluation of the area of interest.

We analyzed the distribution of cervical biopsy and cervigram results using standard contingency table methods based on the χ^2 analysis. The homogeneity χ^2 method tests the null hypothesis that the distribution of biopsies, CIN grade, or acetowhitening is random. A P value less than .05 was taken as rejection of the null hypothesis, suggesting significant heterogeneity related to position.

Results

During the enrollment phase of ALTS, 2773 women underwent a colposcopic examination; 577 of them did not have a biopsy because of poor documentation of the location or results. The remaining 2196 women had a total of 3051 biopsies. The referring cytology was ASCUS for 1380 (62.8%) and LSIL for 816 (37.2%) of these 2196 women, who had a mean age of 26.1 (SD = 7.7, median = 24, range = 18-70), with a mean of 1.6 pregnancies (SD = 1.7, median = 1, range = 0-13). The distribution among women biopsied in the trial included the following: 1499 of the patients (68.3%) had 1 biopsy, 557 (25.4%) had 2 biopsies, and 140 (6.4%) had 3 or 4 biopsies. We excluded 46 biopsies from the analysis because they were considered unsatisfactory or no result was recorded.

Table I Distribution of cervical biopsies by histologic diagnosis and quadrant

Diagnosis	9 o'clock quadrant	12 o'clock quadrant	3 o'clock quadrant	6 o'clock quadrant	Total (n)
Normal					
Row, %	14.8	41.8	16.9	26.4	100
Column, %	57.0	56.2	59.8	51.9	55.6
Number	248	698	284	442	1672
Minor lesions*					
Row, %	13.9	41.7	14.8	29.6	100
Column, %	24.4	25.4	23.6	26.3	25.2
Number	106	316	112	224	758
CIN 2					
Row, %	15.1	35.7	15.5	33.8	100
Column, %	11.0	9.1%	10.3	12.6	
Number	48	113	49	107	317
CIN 3					
Row, %	12.8	44.9	11.6	30.6	100
Column, %	7.6	9.3	6.3	9.3	10.5
Number	33	116	30	79	258
Total					
Row, %	14.5	41.4	15.8	28.4	100
Column, %	100	100	100	100	100
Number	435	1243	475	852	3005

* LSIL, ASCUS.

Table II Percentage of patients with acetowhite lesions by HPV status and histologic diagnosis, o'clock position

Histological diagnosis	O'clock position 1	2	3	4	5	6	7	8	9	10	11	12	*P* value
Normal without any HPV, %	19	16	5	6	8	13	11	7	6	12	18	24	<.001
Normal with oncogenic HPV, %	32	25	16	22	28	30	23	18	18	26	31	39	.006
CIN 1 with oncogenic HPV, %	43	32	25	28	35	36	32	26	24	36	40	44	.018
CIN 3, %	64	56	39	53	62	68	60	57	44	56	69	69	<.001

3 versus 6 o'clock: $P < .05$ in all but CIN 1 group where $P = .09$ (n.s.). 3 versus 12 and 9 versus 12 o'clock: $P < .05$ in all groups. 9 versus 6 o'clock: $P < .05$ in Normal with oncogenic HPV and CIN 3 groups. 3 versus 9 and 6 versus 12 o'clock: $P > .1$ (n.s.) in all but Normal without oncogenic HPV group where 6 versus 12 o'clock: $P < .05$.

The sites of the biopsies by quadrant were not equally distributed; rather there was an increased frequency of biopsies in the 12 o'clock (41.4%) and 6 o'clock (28.4%) quadrants. The 3 o'clock and 9 o'clock quadrants were the least frequently biopsied regions with 15.8% and 14.5% of all biopsies. The distribution of biopsies was not random ($P<.001$). Although the numbers of biopsies varied by quadrant, the distribution of the diagnoses of the cervical biopsies followed the same pattern in each quadrant (Table I, $P = .08$). For example, there was no convincing evidence that a biopsy taken in the most frequently biopsied quadrant, 12 o'clock, was more or less likely to show CIN 2 or CIN 3 than a biopsy taken in the least biopsied quadrant of 9 o'clock.

We used the cervigrams to evaluate whether colposcopists were targeting 12 o'clock and 6 o'clock from convention or convenience rather than because of differential lesion appearance. Table II shows the results from the evaluation of the cervigrams. As expected, the data in Table II demonstrated that worse histological diagnoses were associated with increasingly higher percentages of patients with acetowhite lesions at any position. For each of the 12 clock-face positions, the Mantel χ^2 test for trend showed a statistically significant trend of increasing proportion of women with acetowhite lesions as histology worsened.

With regard to the relative position of acetowhitening, acetowhite areas were more common on the anterior and posterior lips of the cervix (12 o'clock and 6 o'clock positions) than on the lateral lips (3 and 9 o'clock). The differences were seen for women with CIN 3, those with oncogenic HPV-positive CIN 1, and women with oncogenic HPV infection and no histologic abnormality. However, the same pattern was seen for women with no HPV infection.

Because a relative excess of acetowhitening was seen at 12 o'clock and 6 o'clock for women with no HPV infection or histopathologic abnormality, we wished to control for this possible artifact when evaluating whether the distribution of acetowhitening was related to CIN or HPV. Therefore, we recalculated the distributions of acetowhitening in the 3 nonnegative categories (normal with oncogenic HPV, CIN 1 with oncogenic HPV, and CIN 3), subtracting the relative excesses at 12 o'clock and 6 o'clock seen among the HPV-negative, histologically normal women. With this adjustment, no significant differences by clock-face position remained. In other words, the relative excess of acetowhitening at 12 o'clock and 6 o'clock was attributable entirely to an excess that could be seen in the absence of CIN or HPV.

Comment

The goal of colposcopically directed cervical biopsies is to obtain a representative tissue specimen from the suspected, most severe lesion. The process of taking a cervical biopsy is inherently subjective because it relies on the skill of the colposcopist and has been demonstrated to be fairly inaccurate even in the best hands.[13,14] The intent of this analysis was to help understand the topographical distribution of positive cervical biopsies and acetowhite epithelium of the cervix in a large cohort of patients.

Unambiguously, the results of the cervical biopsy data demonstrated that the 12 o'clock and 6 o'clock quadrants are biopsied more frequently as compared with the 3 o'clock and 9 o'clock quadrants. However, the more important question is the reason for the unequal distribution of cervical biopsies. Does this represent a true biologic predilection of the anterior and posterior regions of the cervix for HPV infection and/or neoplastic progression, or is it merely the result of the ease or custom of sampling these locations?

The χ^2 analysis in Table I of the severity of ALTS cervical biopsy results demonstrated that the severity of diagnosis of biopsies, once they were taken, was similar by quadrant. If we had observed a dilution of CIN with increased normal biopsies at 12 o'clock and 6 o'clock, this would have been evidence for biased oversampling in these positions whether because of convenience or custom. However, the even distribution of disease severity by quadrant raises 2 possible explanations that are not necessarily mutually exclusive: (1) all grades of disease may be randomly distributed on the cervix, and the more biopsies taken, anywhere on the cervix, the higher the absolute numbers of abnormalities at the more intensely sampled sites; (2) there may be more disease at 12 o'clock and 6 o'clock leading to more biopsies and higher absolute numbers of abnormalities, but colposcopists are no more accurate in biopsy site identification at 12 o'clock and 6 o'clock so that the yield of disease per biopsy taken is the same as in the 3 o'clock and 9 o'clock quadrants.

The independent finding of more cervicographic abnormalities at 12 o'clock and 6 o'clock among women with underlying CIN 3 suggests, to the extent that acetowhitening itself can be trusted as a diagnostic sign, that there may be more CIN located on the anterior and posterior portions of the cervix as compared with the lateral quadrants.

It is interesting, however, that we found the same uneven distribution of acetowhite areas in the patients with normal histology and negative DNA HPV tests. It is possible that the acetowhitening represented clearing infections. These patients were enrolled in the ALTS study because of an equivocal or cytological manifestation of likely HPV infection; later, at the time of the clinical evaluation, the viral infection might have cleared before the disappearance of acetowhitening. We previously demonstrated that HPV DNA persists after cytologic clearance,[15] but acetowhitening may follow a different time course. Alternatively, it is possible that some portion of the increase in acetowhite lesions on the anterior and posterior cervical lips did not relate to HPV or CIN or cancer risk. If there is such a confounding pattern, it would lead to the conclusion of randomness of acetowhitening, even among women with HPV, low-grade CIN or even CIN 3.

We conclude that more CIN might be located on the anterior and posterior portions of the cervix as compared with the lateral portions. However, the evidence is weak and confounded by an unexplained tendency of the anterior and posterior lips to look more acetowhite, even in the absence of HPV or CIN. Moreover, there is also strong evidence that clinicians exaggerate any true differences by their biopsy practices, which remain, unfortunately, inaccurate and dictated sometimes by ease of biopsy. Recent reports have demonstrated that adding random cervical biopsies at the squamocolumnar junction in areas that have no colposcopically detected lesions increase the detection of CIN 2 or greater by 37.4%, especially in women with HSIL cytology.[16,17] We believe these reports on the increased yield of random biopsies, a practice discredited in the minds of many expert colposcopists, must be evaluated seriously. More generally, the performance of colposcopically directed biopsies must be subjected to more intensive research.

The strengths of this study lie in both the large sample size and the high level of pathology quality control used for the collection and evaluation of the cervical biopsies specimens. This study is the largest study to date to assess this information. The major weakness of this analysis is that ALTS was not designed to examine the distribution of neoplasia arising on the cervix. Specifically, LEEP specimens were not oriented and labeled with sufficient fine detail to permit inclusion in the analysis. A prospective trial specifically designed to address this issue would focus very specifically on the exact location of lesions, would use a rigorous and standardized sectioning protocol for the LEEP specimens, and could incorporate the analysis of immunologic markers to investigate the hypothesis of regional variation in the immune response.

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